2024 Summer Institute In Statistics for Clinical & Epidemiological Research

Module 3:

Design, Conduct, and Analysis of Randomized Clinical Trials with Time to Event Primary Endpoints

Lecture 21:

RCTdesign

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RCTdesign: Raison d'Etre

- Software for design, conduct, and analysis of sequential clinical trials
  - A broad spectrum of group sequential designs
  - A full complement of tools for evaluation of operating characteristics
  - Seamless progression from design to monitoring to analysis
- Extensible, object-oriented language to facilitate
  - Exploration of alternative designs to address needs of individual trials
  - Research into development of new clinical trial methodology

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Clinical Trial Design

- Finding an approach that best addresses the often competing goals: Science, Ethics, Efficiency
  - Basic scientists: focus on mechanisms
  - Clinical scientists: focus on overall patient health
  - Ethical: focus on patients on trial, future patients
  - Economic: focus on profits and/or costs
  - Governmental: focus on safety of public: treatment safety, efficacy, marketing claims
  - Statistical: focus on questions answered precisely
  - Operational: focus on feasibility of mounting trial

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Classical Fixed Sample Designs

- Design stage:
  - Choose a sample size
- Conduct stage:
  - Recruit subjects, gather all the data
- Analysis stage:
  - When all data available, analyze and report

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Group Sequential Designs

- Design stage:
  - Choose an interim monitoring plan
  - Choose a maximal stopping time
    - Statistical information, sample size, calendar time
- Conduct stage:
  - Recruit subjects, gather data in groups
  - After each group, analyze for DMC
    - DMC recommends termination or continuation
- Analysis stage:
  - When study stops, analyze and report

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Group Sequential Approach

- Perform analyses when sample sizes $N_1 \ldots N_J$
  - Can be randomly determined if independent of effect
- At each analysis choose stopping boundaries
  - $a_j < b_j < c_j < d_j$
- Compute test statistic $T_j = T(X_1 \ldots X_{Nj})$
  - Stop if $T_j < a_j$ (extremely low)
  - Stop if $b_j < T_j < c_j$ (approximate equivalence)
  - Stop if $T_j > d_j$ (extremely high)
  - Otherwise continue

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Distinctions without Differences

- Sequential sampling plans
  - Group sequential stopping rules
  - Error spending functions
  - Conditional / predictive power
  - Bayesian posterior probabilities
- Statistical treatment of hypotheses
  - Superiority / Inferiority / Futility
  - Two-sided tests / bioequivalence

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Evaluation of Designs

- Define candidate design constraining two operating characteristics
  - Type I error, power at design alternative
  - Type I error, maximal sample size
- Evaluate other operating characteristics
  - Sample size requirements
  - Power curve
  - Inference to be reported upon termination
  - (Probability of a reversed decision)
- Modify design
- Iterate

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But What If …?

- Possible motivations for adaptive designs
  - Changing conditions in medical environment
    - Approval / withdrawal of competing / ancillary treatments
    - Diagnostic procedures
  - New knowledge from other trials about similar treatments
  - Evidence from ongoing trial
    - Toxicity profile (therapeutic index)
    - Interim estimates of primary efficacy / effectiveness endpoint
      - Overall
      - Within subgroups
    - Interim alternative analyses of primary endpoints
    - Interim estimates of secondary efficacy / effectiveness endpoints

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Adaptive Sampling Plans

- At each interim analysis, possibly modify statistical or scientific aspects of the RCT
- Primarily statistical characteristics
  - Maximal statistical information (UNLESS: impact on MCID)
  - Schedule of analyses (UNLESS: time-varying effects)
  - Conditions for stopping (UNLESS: time-varying effects)
  - Randomization ratios
  - Statistical criteria for credible evidence
- Primarily scientific characteristics
  - Target patient population (inclusion, exclusion criteria)
  - Treatment (dose, administration, frequency, duration)
  - Clinical outcome and/or statistical summary measure

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Adaptive Sample Size Approach

- Perform analyses when sample sizes $N_1 \ldots N_J$
  - $N_1 \ldots N_{J-1}$ can be randomly determined indep of effect
- At each analysis choose stopping boundaries
  - $a_j < b_j < c_j < d_j$
- At $N_1 \ldots N_{J-1}$ compute test statistic $T_j = T(X_1 \ldots X_{Nj})$
  - Stop if $T_j < a_j$ (extremely low)
  - Stop if $b_j < T_j < c_j$ (approximate equivalence)
  - Stop if $T_j > d_j$ (extremely high)
  - Otherwise continue
    - At N_{J-1} determine N_J according to value of T_j

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Implementation in R

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Actual Use

- We use RCTdesign to narrow the search for useful group sequential designs
  - Typically specify type I error and
    - Design alternative and desired power OR
    - Design alternative and maximal sample size OR
    - Maximal sample size and desired power
  - Search through a family of stopping boundaries
    - Alternative criteria for early stopping: null, alternative, both
    - Alternative degrees of “early conservatism”
    - Alternative number and schedule of analyses
- We use RCTdesign to evaluate operating characteristics
  - Different operating characteristics of interest to different collaborating disciplines

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Implementation in R: Basic Objects

- seqModel
  - Probability model for primary endpoint
  - Statistical analysis model
- seqBoundary
  - A stopping rule (on some scale)
- seqOperatingChar
  - Stopping probabilities
  - Power (including type I error)
  - Sample size distribution
- seqInference
  - Point estimates, confidence intervals, P values

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Implementation in R: Basic Objects (Survival)

- seqPHAccrual
  - Describes parameters for subject accrual
  - Number of subjects accrued
  - Administrative censoring: Distribution of entry times
  - Potentially informative censoring: Distribution of dropout times
  - Additional follow-up time
- seqPHNSubjects
  - Summarizes number of subjects accrued and at risk

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Implementation in R: High Level Objects

- seqDesign
  - Probability model for primary endpoint
  - Statistical hypotheses
  - Design parameters to specify a boundary
  - Stopping boundaries
  - Survival: Accrual and risk set information
- seqMonitor
  - A group sequential design
  - Interim data
  - Updated monitoring boundaries
  - Statistical inference

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Implementation in R: Operations

- Creation of objects
  - User interface to facilitate scientific interpretations
  - (Graphical user interface (GUI) under development)
- Printing objects
  - Information necessary for protocols, statistical analysis plans
- Plotting objects
  - Facilitate comparisons among candidate designs
- Updates of objects

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Basics: Probability Model

- The primary clinical outcome of a RCT is summarized by θ
- Common choices for θ in two arm studies
  - Difference (or ratio) of means
  - Ratio of geometric means
  - Difference (or ratio) of proportions having some event
  - Ratio of odds of having some event
  - Ratio (or difference) or rates of some event
  - Ratio of hazards (time averaged?)
- Note that all of the above can be analyzed in (nearly) a distribution-free manner
  - Sums used in the statistics mean that CLT provides good approximation

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Stopping Boundary Scales

- Boundary scales (1:1 transformations among these)
  - Z statistic
  - P value
    - Fixed sample (so wrong)
    - Computed under sequential sampling rule (so correct)
  - Error spending function
  - Estimates
    - MLE (biased due to stopping rule)
    - Adjusted for stopping rule
  - Conditional power
    - Computed under design alternative or arbitrary choice
    - Computed under current MLE
  - Predictive power
    - Computed under flat prior (possibly improper) or arbitrary normal prior

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Basics: Defining a Scale

- `seqScale (`
  `scaleType` : a code for which boundary scale
  ("S", "X", "Z", "P", "E", "C", "H")
  `threshold` : optional argument used for some scales
  `hypTheta` : optional argument used for some scales
  `priorTheta` : optional argument used for some scales
  `priorVariation` : optional argument used for some scales
  `pessimism` : optional argument used for some scales
  `boundaryNumber` : optional argument used for some scales
  `scaleParameters` : optional argument used for some scales
  `)`

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Basics: Creating a Stopping Boundary

- `seqBoundary (`
  - `x` : a *J* by 4 matrix of stopping thresholds
  - `scale` : (a code for) which boundary scale
  - `sample.size` : a *J* vector of sample sizes at analysis times
  - `no.stopping` : optional argument used for display
  - … : additional arguments to define boundary scales
  - `)`

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Basics: Creating a RCT Design (partial)

- `seqDesign (`
  - `prob.model` : probability model for primary endpoint
  - `arms` : number of arms (1,2,… or 0 for regression)
  - `null.hypothesis` : a vector (length corresponds to arms)
  - `alt.hypothesis` : a vector (length corresponds to arms)
  - `variance` : a vector (length corresponds to arms)
  - `ratio` : a vector (length corresponds to arms)
  - `sample.size` : a vector of sample sizes at analysis times
  - `test.type` : "greater", "less", "two.sided"
  - `exact.constraint` : a stopping boundary
  - `display.scale` : boundary scale for display
  - `(many others)` : many other arguments for design families and accrual parameters for survival
  - `)`

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Basics: Operating Characteristics

- `seqOC (`
  - `x` : a seqDesign object
  - `theta` : alternatives for operating characteristics
  - `how.many` : used if theta and power not supplied
  - `range.theta` : used if theta and power not supplied
  - `power` : specification of theta via power
  - `upper` : indicator that upper power curve desired
  - `lower` : indicator that lower power curve desired
  - `)`
- Plotting functions
  - `seqPlotASN (x, … )`
  - `seqPlotPower (x, … )`
  - `seqPlotStopProb (x, … )`

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Additional Resources

- www.RCTdesign.org
  - SS Emerson, DL Gillen, JM Kittelson, GP Levin, SC Emerson
- Software
  - Documentation
  - Tutorials
  - Extensions (Bayesian evaluation; adaptive design evaluation)
- Learning
  - Short courses
  - Research talks
  - Case studies
- Methodology
  - Technical reports on a variety of RCT-related topics

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